Procter&Gamble
PHARMACEUTICALS

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19 April 1999

Documents Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane.
Rm 1061
Rockville, MD 20852

Re: Docket Number 99D-0121

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the draft Guidance for Industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System.* We have the following suggestions and comments:

III.C Dissolution

1. It is not clear if the criteria for *rapid dissolving* relates to mean or individual results. We believe it should relate to the average of 12 tablets.

2. Dissolution for rapidly dissolving materials would ordinarily be tested using Apparatus I or Apparatus II. However there may be instances where another apparatus would be appropriate. We suggest adding a sentence that says "The suitability of other apparatuses should be discussed with FDA and justified."

IV.A Determining Solubility Class

Unless the pH-solubility characteristics of the drug are very complex, requiring solubility at eight or more pH values is not necessary. We suggesting rewording the third sentence to say "Four to eight pH conditions depending on the ionization/solubility characteristics of the drug should be evaluated." For a non-ionizable drug a pH profile should not be necessary.

IV.B. Determining Permeability Class

Delete the last sentence of paragraph 1 which indicates that information such as octanol:water partition coeficients should be provided. The Permeability Class will be determined from absorption studies or intestinal permeability. The octanol:water information may be interesting, but not required for the determination of the Permeability Class. If that sentence is retained, using the word "determined" would be clearer than the word "derived".

99D-0121

C3

IV.B.1 Studies of the Extent of Absorption in Humans

1. Third sentence: Revise to say "For mass-balance studies ... samples should be collected for a period of time equivalent to 97% of the total AUC."

2. Delete the sentence that starts "Serial samples of exhaled air ... " This should be determined in animal studies before the human studies are run.

   For clarity, insert the following before the sentence that starts "The done-normalized ratios of cumulative urinary recovery ...": "If different IV and oral doses are administered."

3. For drugs that undergo a significant first pass effect, the use of the ratio of urinary recovery of radioactivity (oral/intravenous) to assess extent of absorption may not be appropriate. Consider the following example:

   A metabolite, primarily formed during "first pass" (e.g. intestinal metabolism), exists as a major metabolite following oral administration but it is a minor metabolite following iv administration. If the metabolite(s) formed during "first pass" is preferentially cleared renally whereas those metabolites formed systematically are primarily eliminated in feces, one may find a similar urinary and fecal recovery of radioactivity, even with low oral absorption. Under these circumstances, the use of urinary radioactivity recovery may overestimate absorption, especially when significant fecal recovery exist following intravenous administration. As such, the assumption of similarity of metabolic profiles (e.g., AUCm/AUC) or Clr/Cl of the metabolites when metabolic profiles differ, needs to be demonstrated prior to using the ratio of urinary recovery of radioactivity following oral to intravenous administration.

IV.B.2. Intestinal Permeability Methods

A correlation should be established using 20 or more compounds that include poorly, moderately, and well absorbed compounds (not just complete or poor absorption markers). In particular, if a ratio of the test drug permeability to an internal standard permeability is used to determine high permeability potential of the test compound, the internal standard should be chosen so that it is near the inflection part of the permeability-absorption correlation curve, i.e. transition from poor to good absorption, and has a minimum mean absorption of 90%. If it is too far right of the inflection in the curve, one may underestimate the absorption potential of the test compound if they rely solely on the ratio of test compound to internal standard.

An improved means to determine the absorption potential of a test material would be to:

1. Determine the permeability/absorption relationship using a variety of compounds with absorptions from 0 to 100% with a minimum number of moderately absorbed compounds to define the transition of poor to well absorbed compounds; and

2. Determine the least-squares non-linear regression relationship for the model defined above (this should be based on an absorption vs. permeability ratio of the test compound and an internal standard). The resultant equation could then be used to calculate the absorption potential of the test compound (see for example: Pharm Res 14:1792 (1997)).

IV.B.2. Intestinal Permeability Methods (continued)

Some additional comments on paragraph 3 are the following:

1. Some criteria for comparing the permeability of two compounds is needed, e.g., numbers of replicates, confidence intervals, etc.

2. This section should say "A low permeability internal standard is <u>needed</u> to ensure intestinal membrane integrity", rather than <u>suggested</u>.

V. 3.

The criteria for the f2 metric should be 50 to 100 to be consistent with SUPAC IR.

If there are any questions or if I can be of further assistance, feel free to contact me.

Sincerely,

Harry L. Welles

Harry L. Welles, Ph.D.
Principal Scientist
Regulatory Affairs

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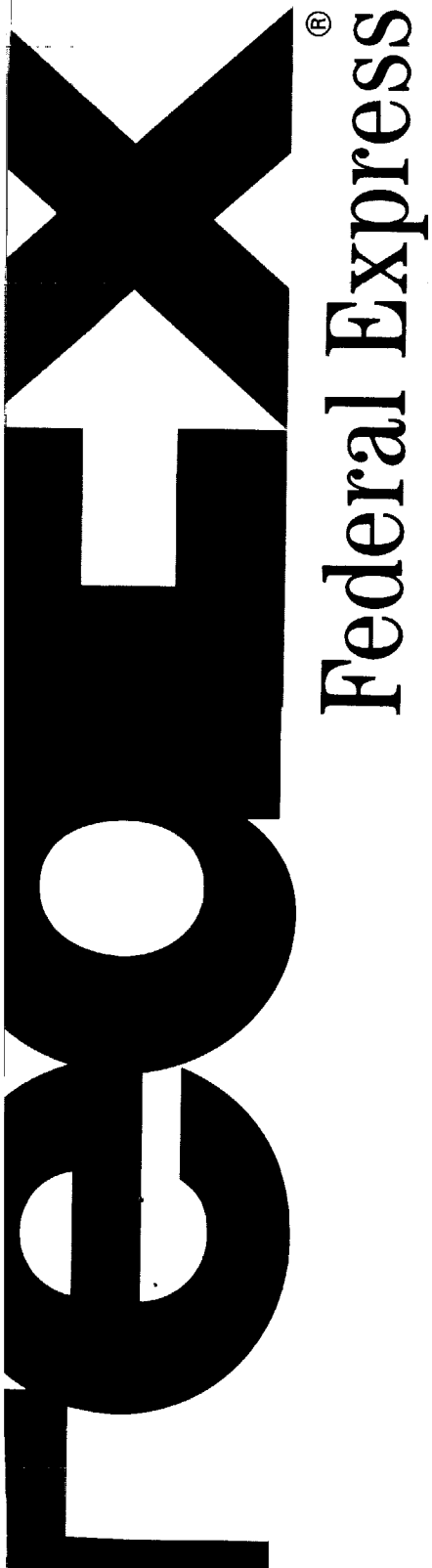

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